

permitted on the market unless it can be proved by rigorous experiment to alter the course of some ailment or disease; that is, it must be effective."<sup>1</sup> And one can easily see, the cost squeeze being what it is, that this approach may soon be applied to just about anything and everything doctors do for their patients. Not only drugs but services and procedures, whether in office, hospitals or elsewhere, may be subjected to the same test of scientific proof of effectiveness—and this is likely to be persuasive.

This writer is troubled by so rigorous a scientific approach. On the one hand as physician scientists we instinctively support this position. It will go against the scientific grain to justify the use of a pill, or a service, or a procedure unless we can show that it is effective. But there is a gnawing feeling that there is something wrong here. Putting aside the obvious question of whether we know enough yet to require scientific proof of the effectiveness of everything we do in patient care, there seems to be something else important which has been left out. Perhaps there is a clue in the second trend, the trend to seek and accept alternative methods of care, which in many cases seems to be almost a revolt against scientific medicine. Somehow, scientific medicine as we practice it today does not seem to satisfy patients and the public as well as did the old time "horse and buggy" doctor of the prescientific era. Clearly medicine is losing something, or has lost it.

This something we are losing or have lost is obviously not science. We have more and better science than ever. If it is not science, then it must be what used to be called the art, but which now seems to lack definition or description, or even much genuine interest. Experienced clinicians know what this something is, and patients and the public seem to sense it. And in the present stage of our knowledge and understanding it is not something that can be proved effective or not effective by rigorous experiment. We will need to have far more knowledge in the social and behavioral sciences and a much better comprehension of the human environment before this can be done. What seems really needed is much more emphasis on the teaching and practice of the art, in the face of professional preoccupation with the science and public preoccupation with feeling better in a tense, stressful and far too polluted world—with which many people find it difficult to cope.

There is danger now that the regulatory authorities in their frantic need to curtail costs, will, by seeking proof of effectiveness by rigorous experiment or otherwise, unwittingly deprive physicians of some essential tools of the art which they should probably be using more, not less. These tools are medicines that do no harm and the services of caring and concern, in addition to those of curing. In a sense medicine may be approaching an intersection in the road just ahead, where it may continue on what is still the relatively undeveloped country road of medical science, or rejoin the highway, where most of the traffic is, by once again embracing the whole of patient care—that is, care of the whole patient. In our present state of knowledge, medicine is without question still an art as well as a science, and the time has come when this needs more than just lip service. If we are to do this, the strict scientific approach must be leavened with a recognition that it will be a long time, if ever, before everything in patient care can meet the standard of scientific proof by rigorous experiment.

—MSMW

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#### EDITORIAL REVIEW

## Progress With Hepatitis B Virus

RECENT RESEARCH with hepatitis B virus (HBV) emphasizes that this is a unique virus in several interesting ways; and as in all research, experimental results have continued to raise many new questions as old questions are answered. Gitnick's review in this issue covers some of the new ground and here I will only point out several of the unanswered questions about the nature and behavior of this important virus. One question concerns the identity of the infectious form of the virus. The failure so far to infect tissue culture cells or convenient experimental animals has prevented development of assays for infectious HBV short of transmission to man or the few other susceptible higher primates such as chimpanzees. The current methods for infectivity testing are so cumbersome that it has not yet been possible to directly identify the infectious particle. However, one form of

hepatitis B surface antigen (HB<sub>s</sub>Ag) found in the blood, the Dane particle, has several properties suggesting that it may be the infectious particle: (1) its surface antigen (HB<sub>s</sub>Ag) appears to react with antibody (anti-HB<sub>s</sub>) shown to protect patients against HBV infection,<sup>1</sup> (2) it contains a unique internal core antigen (HB<sub>c</sub>Ag) which is probably virus specified,<sup>2</sup> (3) its size<sup>3</sup> is consistent with estimates of the size of infectious HBV determined by ultrafiltration,<sup>4</sup> (4) its concentration in most sera<sup>5</sup> is consistent with titrations of infectivity in serum,<sup>6</sup> (5) its concentration in sera appears to correlate with the probability that patients will transmit infection to contacts,<sup>7,8</sup> (6) purified and concentrated preparations of Dane particles have been shown to be infectious at higher dilutions than previously shown for unfractionated HB<sub>s</sub>Ag positive serum,<sup>9</sup> (7) it is the only viral antigen form known to contain nucleic acid<sup>10</sup> and (8) deoxyribonucleic acid (DNA) reassociation experiments have shown that Dane particle DNA base sequences are only present in the DNA and ribonucleic acid (RNA) of infected liver and not in uninfected liver, and these sequences appear to be covalently attached to high molecular weight DNA<sup>11</sup> as are other viral DNA's when integrated into chromosomal DNA.

If Dane particles are hepatitis B virions, their ultrastructure, antigenic composition and other properties indicate that HBV is not a member of any known group of viruses but is a unique virus, and its structure is more complex than that of many simple viruses. Among the unique properties are the size and structure of the small circular DNA within the core of Dane particles and the presence of a DNA polymerase in the core.<sup>10</sup> The circular DNA molecule is double stranded over approximately two thirds of its length and the remainder is single stranded.<sup>12,13</sup> The DNA polymerase reaction closes the single stranded gap to make fully elongated double stranded circular DNA molecules of 3,200 nucleotide pairs. This is smaller than the double stranded DNA found in any other virus and such a molecule could specify no more than three or four average sized proteins. Its small size raises a question of whether a single Dane particle DNA molecule could contain the entire genome of a virus with a structure as complex as that of the Dane particle. The answer to this question must remain until the number and sizes of the HBV genes (or gene products) is known. The function of the single stranded region in this DNA molecule and

the utility of the DNA polymerase for HBV are not known and remain central questions for understanding how this virus replicates and interacts with infected cells. No other viruses possess these interesting features.

Another important question concerns the relationship of the complex of antigens referred to collectively as "e" antigens or HB<sub>e</sub>Ag to HBV. These antigens are physically and antigenically distinct from HB<sub>s</sub>Ag and HB<sub>c</sub>Ag particles. Whether HB<sub>e</sub>Ag is an HBV gene product is not settled, although its occurrence exclusively in HB<sub>s</sub>Ag positive sera<sup>6</sup> and the frequent antibody response to HB<sub>e</sub>Ag following HBV infection are most consistent with this possibility. HB<sub>e</sub>Ag has proven difficult to purify so that it has not been well characterized chemically. An intriguing feature of HB<sub>e</sub>Ag is its common occurrence in sera of chronic HB<sub>s</sub>Ag carriers with high concentrations of Dane particles<sup>7,8</sup> and therefore its presence correlates (as do Dane particles) with a propensity for transmission of HBV infection from chronic carrier mothers to newborns<sup>7</sup> and from carriers to contacts accidentally inoculated with contaminated needles.<sup>8</sup>

Their regular occurrence together suggests that HB<sub>e</sub>Ag and Dane particles (and HBV) may be related in some direct way. It has been reported that anti-HB<sub>e</sub> reacts with the surface of Dane particles<sup>15</sup> suggesting that HB<sub>e</sub>Ag may be a surface component of Dane particles. However, the antiserum used in that study was not proved to be monospecific and other investigators have failed to confirm that finding. It seems more likely that if HB<sub>e</sub>Ag is a component of Dane particles it is an internal component, although it is known to be distinct from HB<sub>c</sub>Ag. The question of its physical relationship to Dane particles remains unsettled.

Recently, Neurath and Strick<sup>16</sup> have reported that HB<sub>e</sub>Ag has properties similar to those of immunoglobulin IgG4 and have proposed that HB<sub>e</sub>Ag is an antibody formed in response to HBV infection and which possesses idiotypic antigenic determinants to which anti-HB<sub>e</sub> is directed. If this hypothesis is correct, HB<sub>e</sub>Ag would not represent HBV specified polypeptide. Attempts to confirm the hypothesis have led others to the conclusion that HB<sub>e</sub>Ag is probably not an immunoglobulin and more work will be required to establish or refute the hypothesis.

Another recent report<sup>17</sup> suggests that anti-HB<sub>e</sub> inhibits lactic dehydrogenase (LDH) activity by

complexing with the enzyme in serum, raising the possibility that HB<sub>e</sub>Ag is a host component or exists as a complex with LDH in serum. This report is yet to be confirmed by others. The widely different findings concerning HB<sub>e</sub>Ag in the studies cited above emphasize the difficulties encountered with investigation of HB<sub>e</sub>Ag. Although the nature of HB<sub>e</sub>Ag remains unclear, its presence (like that of Dane particles) in serum may be clinically useful for identifying patients with a high probability of infectiousness for contacts and possibly those with underlying liver disease.

Clearly one of the most fascinating biological features of HBV is the relatively common occurrence of persistent infection in which virus forms circulate in the blood in very high concentrations often for many years. HBV persistence contrasts sharply with other persistent infections of man such as those with herpes viruses in which continuous viremia is not present and periods of inapparent or latent infection predominate. Continuous viremia does occur during persistent infection with certain other animal viruses, however. The closest parallel appears to be some persistent infections with oncornaviruses such as avian and murine leukemia viruses (ALV and MLV), other retroviruses such as equine infectious anemia virus (EIAV) and arena viruses such as lymphocytic choriomeningitis virus (LCM) in mice. In contrast to HBV, all are RNA viruses. A striking difference with the other viruses would appear to be that the predominant viral form in the blood in persistent HBV infection is incomplete virus in the form of particles of virus coat antigen (HB<sub>s</sub>Ag) and in the case of the other viruses numerous incomplete viral forms have not been observed. The biological significance of the defective virus forms in HBV infection is not clear. No defective forms with the properties of the defective-interfering or DI particles (that is, containing viral nucleic acid with deletions) found with almost all well studied viruses<sup>18</sup> have been recognized in the case of HBV. The potential relevance of DI particles for persistent HBV infection is that they play a role in maintaining persistent infections in some model systems with other viruses.<sup>19</sup>

The medical importance of persistent HBV infection is that it represents a source of virus for transmission from patients to their contacts and for perpetuation of this virus which has no known animal reservoir, and because of associated hepatic and extrahepatic diseases. In certain under-

developed areas where HB<sub>s</sub>Ag carrier rates may exceed 5 percent or 10 percent of the population, neonatal transmission from persistently infected mothers may be a particularly important mode of virus transmission. Persistent viremia would also appear to be a favorable condition for transmission by blood feeding insects such as mosquitos. Although some populations of mosquitos have been shown to contain HB<sub>s</sub>Ag,<sup>20</sup> no direct evidence of transmission to man by mosquito vectors has been reported and this possibility deserves investigation.

One important question about HBV infections is the mechanisms which permit infection to persist indefinitely in many cases. In the case of ALV<sup>21,22</sup> and LCM<sup>23,24</sup> which do not appear to be cytopathic for their hosts, infection at very young ages and immunosuppression have been shown to favor persistent infection without associated disease. Evidence suggests that persistence in these cases results from a relative or partial immunological tolerance to the virus.<sup>21-24</sup> Disease associated with persistence of these viruses under some conditions is related to the immune response to the virus and not a direct cytopathic effect of the virus.<sup>25</sup> Very young age, immunosuppressing chemotherapy and diseases such as chronic lymphocytic leukemia, Down syndrome and lepromatous leprosy appear to be associated with an increased incidence of virus persistence after HBV infection. In addition, low infecting doses of HBV have been shown to result in long incubation periods, mild initial disease and frequent persistent infection.<sup>26</sup> A common denominator leading to persistent infection could be a modified or inadequate immune response to HBV under each of these conditions and this possibility must be investigated. Frequent persistent infection in the absence of liver disease suggests that HBV is probably not cytopathic for hepatocytes.

A wide spectrum of hepatic and extrahepatic disease may, however, be associated with persistent HBV infections. Polyarteritis,<sup>27</sup> glomerulonephritis,<sup>28</sup> infantile papular acrodermatitis,<sup>29</sup> cryoglobulinemia<sup>30</sup> and polymyalgia rheumatica<sup>31</sup> have been described in association with persistent HBV infection. The findings in well studied cases of extrahepatic disease are consistent with tissue damage mediated by HB<sub>s</sub>Ag immune complex deposition. Further study is needed to clarify the pathogenesis of these syndromes and if HB<sub>s</sub>Ag-

antibody complexes prove to be necessary for disease, the process should in theory be controlled by suppression of HB<sub>s</sub>Ag formation.

The pathogenesis of hepatic diseases such as chronic active hepatitis (CAH) and chronic persistent hepatitis (CPH) associated with persistent HBV infection is not as clear. Immune cell mediated tissue injury is a likely mechanism although direct evidence supporting this possibility is not abundant. An unexplained association in persistent HBV infections is the more frequent occurrence of Dane particles and HB<sub>e</sub>Ag in patients with hepatic disease compared with patients without disease.<sup>14,32</sup> The role these factors play in hepatic disease requires further study including assessment of the cellular immune response to HB<sub>e</sub>Ag and the antigen unique to Dane particles, HB<sub>c</sub>Ag.

Epidemiologic data are consistent with HBV having a central role in hepatocellular carcinoma in areas of the world where persistent HBV infection is common.<sup>33</sup> A direct role of the virus in carcinogenesis can only be proven by studies of the relationship of the virus and the tumor cell, tests of the ability of the virus to transform cells and studies of the effect of virus control program (for example, by vaccination) on the occurrence of this tumor in high-risk populations.

A final area of research where questions remain concerns methods for treatment and prevention of HBV infection. By far the most effective approach for control of HBV so far has come from the ability to use HB<sub>s</sub>Ag to identify infected patients and prevent transmission of virus by blood transfusion and other routes. The effectiveness of hyperimmune anti-HB<sub>s</sub> in preventing infection is not completely clear because it has been compared with immune globulin containing anti-HB<sub>s</sub> in prospective trials (such as Grady's study<sup>34</sup>) rather than with inert placebo. Because some trials (although not all) suggested effectiveness and its use was subsequently recommended, a prospective comparison with a true placebo is not now feasible and the degree of its effectiveness may never be thoroughly determined.

Vaccine development is well underway. Initial studies using purified HB<sub>s</sub>Ag particles in chimpanzees suggest that protection can be achieved.<sup>1</sup> Trials of this vaccine in man are underway. If it proves to be safe and effective in man, a vaccine could be useful for protection of certain high-risk populations.

Attempts to favorably affect the course of acute and chronic hepatitis B with hyperimmune anti-

HB<sub>s</sub>, transfer factor and some antiviral drugs have been unsuccessful. Two antiviral substances, however, have recently been shown to inhibit production of Dane particles in persistently infected patients. Human leukocyte interferon<sup>35</sup> and adenine arabinoside (ara-A)<sup>36</sup> have been shown to rapidly inhibit Dane particle production in all patients treated. Extension of the studies by these investigators to additional patients has shown the effect to be permanent in some patients and reversible in others. HB<sub>e</sub>Ag titers have irreversibly fallen in some patients during and following treatment. All evidence of virus infection in liver and blood cleared during interferon treatment of two female patients who have remained free of infection since treatment ended. Although these results are encouraging, only further studies including prospective controlled trials will determine the frequency and extent of the effects of such treatment.

HBV continues to be an important pathogen for man and interesting questions about its unique biology as well as the clinical challenge of its control remain.

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## Newborn Infants With Congenital Heart Disease

WITHIN the past decade the attention of pediatric cardiologists and cardiovascular surgeons has shifted increasingly toward early infancy. Robert Gross' first patients, operated upon for patent ductus arteriosus 40 years ago, were school age children, and the first edition of Helen Taussig's book, published 30 years ago, advised cardiofo- gists to postpone shunt operations, whenever possible, to beyond two years of age. By contrast, according to data from the New England Regional Infant Cardiac Program (NERICP), 28 percent of infants with cardiac problems admitted to a center between 1968 and 1974 were less than 2 days old and 29 percent of those operated upon were less than a week old.

The reason for this shift in emphasis from children and adolescents to infants and newborns is, first of all, the recognition that the vast majority of those who die within the first two decades with congenital heart disease will do so within the first year of life—actually within the first three months of life. The advances in surgical skills and diagnostic techniques represent the means through which pediatric cardiac surgeons and their cardiologist colleagues can respond to the challenge of high mortality in the very young. Furthermore, improved case finding, resulting from efforts at regionalization of neonatology as well as pediatric cardiology, allows more babies, at younger and younger ages, to reach cardiac centers. Finally, and the effect of economics on these matters should not be underestimated, the backlog of common congenital malformations in children and adolescents having been cleared up, cardiologists and cardiac surgeons are looking for new fields to conquer.

Since, for a variety of reasons, pediatric cardiology has become infant or even neonatal cardiology, the specialty conference this month by Kirkpatrick and co-workers on the differential diagnosis of congenital heart disease in the newborn is timely. Although the discussion of this complex problem is clear, concise and generally helpful, a few comments on the specifics may be indicated.

As to the five cardinal findings of significant heart disease, the writer of this editorial believes that tachypnea and cyanosis should be emphasized first and foremost as indicators of critical heart disease in infancy. Murmurs, by themselves, are in most instances of secondary importance. It is well to emphasize that some of the sickest infants with heart disease may have no murmurs at all (transposition of the great arteries, total anomalous venous return, and so forth) and some of the loudest murmurs may represent trivial malformations (small ventricular septal defect, minimal pulmonic stenosis). Acute congestive heart failure is most commonly manifested by tachypnea in newborns, whereas the more chronic failure, in late infancy, may be characterized by severe failure to thrive. Peripheral edema almost never occurs in the very young, except rarely with coarctation of the aorta. Hepatomegaly, as well as gallop rhythm, are ancillary evidences of congestive heart failure; the clinical diagnosis is based primarily on the findings of tachypnea not explained by pulmonary disease and significant car-